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(54) Title: ALPHA–KETO OXADIAZOLES AS SERINE PROTEASE INHIBITORS

(57) Abstract

The present invention relates to certain substituted oxadiazole, thiadiazole, and triazole peptoids containing valine and proline residues and nonpeptoids containing pyrimidinone residues useful as inhibitors of serine proteases, for example human neutrophil elastase (HNE). Compounds of the present invention are useful for the treatment or amelioration of symptoms of adult respiratory distress syndrome, septic shock, and multiple organ failure. Processes mediated by HNE are also implicated in conditions such as arthritis, periodontal disease, glomerulonephritis, and cystic fibrosis.

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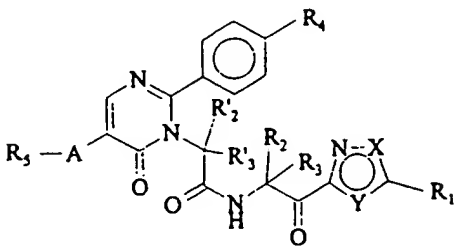
In another embodiment, the present invention provides compounds of formula II:



II

wherein X and Y are independently O or N;

R_1, R_2, and R_3 are as above;

R'_2 and R'_3 are independently H or alkyl; or together form a ring consisting of 3-5 carbon atoms in which one or more carbon atoms of the ring can optionally be replaced by heteroatoms selected from O, S or N,

wherein N is optionally substituted with H or alkyl;

A is a direct bond, -NH- or -OC(O)-NH-;

R_4 is H or halo; and

R_5 is H, alkyl or arylalkyl; or

a pharmaceutically acceptable salt thereof.

Preferably, compounds of this embodiment of the present invention comprise a 1,3,4 oxadiazole ring (i.e., X is N; Y is O).

In one preferred embodiment of the invention, R_1 is alkyl, such as *tert*-butyl. In another embodiment, R_1 is α,α-dialkylalkyl fused aryl-cycloalkyl wherein the cycloalkyl group is substituted with two O atoms, such as an α,α-dimethyl-(3,4-methylenedioxy)benzyl group. In yet another embodiment, R_1 is α,α-dialkylalkylaryl, such as an α,α-dimethylbenzyl group. In still another preferred embodiment, R_2 and R_3 are independently alkyl, such as isopropyl, or H. In a more preferred embodiment, R_2 is isopropyl, R_3 is H, and R_2' and R_3' are both H. Where R_4 is halo, R_4 may be Cl, F, I or Br, although preferably it is F.

As used herein, the term "optionally substituted" means, when substituted, mono to fully substituted.

As used herein, the term "independently" means that the substituents may be the same or different.

As used herein, the term "alkyl" means C_1-C_{15}, and preferably C_1-C_8. It will be understood that the alkyl group may be linear or branched.

As used herein, the term "α,α-dialkylalkylaryl" means that the alkyl groups are substituted at the α-positions to the oxadiazole ring or to the aryl group or both. One such example is an α,α-dialkylbenzyl, wherein the α-substituents are preferably methyl, ethyl or propyl. A specific example is α,α-dimethylbenzyl. The term "α,α-dialkylalkyl fused aryl-cycloalkyl" is defined to mean that the alkyl groups are substituted at the α-positions to the oxadiazole ring or to the aryl group, and a cycloalkyl is fused to the aryl ring. One such example of an "α,α-dialkylalkyl fused aryl-cycloalkyl" is an α,α-dialkyl-3,4-methylenedioxybenzyl group, wherein the α-substituents are preferably methyl, ethyl or propyl; preferably they are methyl. A specific example includes the α,α-dimethyl-3,4-methylenedioxybenzyl group.

As used herein, the term alkyloxycarbonyl means alkyl-O-C(O)- wherein the meaning of alkyl is defined above. One such example of an alkyloxycarbonyl is methyloxycarbonyl and is defined by the formula CH_3-O-C(O)-.

Brief Description of the Drawings

Figure 1 is a schematic representation of the synthetic scheme for the Boc protected amino alcohol intermediates used in the invention.

Figure 2 is a schematic representation of the synthetic scheme for the compounds of one embodiment of the invention.

Figure 3 is a schematic representation of the synthetic scheme for the compounds of another embodiment of the invention.

Detailed Description

The compounds of the present invention have been found to be potent inhibitors of the serine protease human neutrophil elastase (HNE). They are reversible inhibitors that presumably form a transition state intermediate with the active site serine residue. The compounds are characterized by their low molecular weights, high selectivity with respect to HNE and stability regarding physiological conditions. Therefore, the compounds can be implemented to prevent, alleviate and/or otherwise treat diseases, which are mediated by the

ALPHA-KETO OXADIAZOLES AS SERINE PROTEASE INHIBITORS

This application claims the benefit of the filing date of U.S. Serial No. 09/090,046and U.S. Serial No. 09/090,274, filed June 3, 1998; both of which are incorporated herein by reference.

Background of the Invention

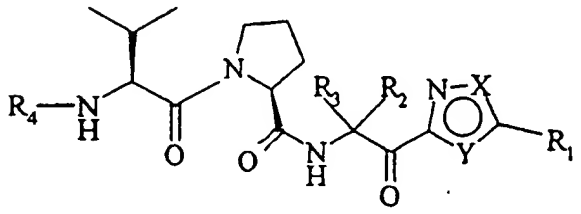
The serine proteases are a class of enzymes, which includes elastase, chymotrypsin, cathepsin G, trypsin and thrombin. These proteases have in common a catalytic triad consisting of Serine-195, Histidine-57 and Aspartic acid-102(chymotrypsin numbering system). Human neutrophil elastase (HNE) is a proteolytic enzyme secreted by polymorphonuclear leukocytes (PMNs) in response to a variety of inflammatory stimuli. This release of HNE and its extracellular proteolytic activity are highly regulated and are normal, beneficial functions of PMNs. The degradative capacity of HNE, under normal circumstances, is modulated by relatively high plasma concentrations of α_1-proteinase inhibitor (α-PI). However, stimulated PMNs produce a burst of active oxygen metabolites, some of which (hypochlorous acid for example) are capable of oxidizing a critical methionine residue in α-PI. Oxidized α-PI has been shown to have limited potency as an HNE inhibitor and it has been proposed that alteration of this protease/antiprotease balance permits HNE to perform its degradative functions in localized and controlled environments.

Despite this balance of protease/antiprotease activity, there are several human disease states in which a breakdown of this control mechanism is implicated in the pathogenesis of the condition. Improper modulation of HNE activity has been suggested as a contributing factor in adult respiratory distress syndrome, septic shock and multiple organ failure. A series of studies also have indicated the involvement of PMNs and neutrophil elastase in myocardial ischemia-reperfusion injury. Humans with below-normal levels of α_1-PI have an increased probability of developing emphysema. HNE-mediated processes are implicated in other conditions such as arthritis, periodontal disease, glomerulonephritis, dermatitis, psoriasis, cystic fibrosis, chronic bronchitis, atherosclerosis, Alzheimer's disease, organ transplantation, corneal ulcers, and invasion behavior of malignant tumors.

There is a need for effective inhibitors of HNE as therapeutic and as prophylactic agents for the treatment and/or prevention of elastase-mediated problems.

Summary of the Invention

In one embodiment, the present invention provides compounds of formula I



(I)

wherein X and Y are independently O or N;

R_1 is alkyl, α,α-dialkylalkylaryl or α,α-dialkylalkyl fused aryl-cycloalkyl wherein the cycloalkyl group is optionally substituted with two or more O atoms;

R_2 and R_3 are independently H or alkyl; or together form a ring consisting of 3-5 carbons in which one or more carbon atoms of the ring can optionally be replaced with heteroatoms selected from O, S or N wherein N is optionally substituted with H or alkyl, preferably one of R_2 and R_3 is H and the other is *iso*-propyl; and

R_4 is alkyloxycarbonyl.

Preferably, compounds of the present invention comprise a 1,3,4 oxadiazole ring (i.e., X is N; Y is O).

In one preferred embodiment of the invention, R_1 is alkyl, such as *tert*-butyl. In another embodiment, R_1 is α,α-dialkylalkylaryl, such as an α,α-dimethylbenzyl group. In still another preferred embodiment, R_1 is α,α-dialkylalkyl fused aryl-cycloalkyl wherein the cycloalkyl group is substituted with two O atoms, such as an α,α-dimethyl-(3,4- methylenedioxy)benzyl group. In yet another preferred embodiment, R_2 and R_3 are independently alkyl, such as isopropyl, or H. Preferably, R_2 is isopropyl and R_3 is H.

degradative effects associated with the presence of HNE. Their usage is of particular importance as they relate to various human treatment *in vivo* but may also be used as a diagnostic tool *in vitro*.

The present invention provides, but is not limited to, specific embodiments set forth in the Examples as well as those set forth below.

The nomenclature for the embodiments is as follows (although embodiments disclosed indicate the stereochemistry of the 2-methylpropyl group as having the *(S)*-configuration, it will be understood that both the enantiomerically pure *(R)* and racemic *(R,S)* configurations are within the scope of the invention):

Example 1 Methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(*tert*-butyl)-oxadiazolyl]carbonyl)-2-*(S)*-methylpropyl]-*L*-prolinamide.

Example 2 Methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(α,α-dimethylbenzyl)-oxadiazolyl]carbonyl)-2-*(S)*-methylpropyl]-*L*-prolinamide.

Example 3 Methyloxycarbonyl-*L*-valyl-*N*-[1 -(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)- 1,3,4-oxadiazolyl]carbonyl)-2-*(S)*-methylpropyl]-*L*-prolinamide.

Example 4 2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-*tert*-butyl 1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide.

Example 5 2-[5-Benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl) 1,6-dihydro-1- pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide.

Example 6 2-[5-Amino-6-oxo-2-(4-fiuorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide.

Example 7 2-[5-Benzyloxycarbonylamino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[l-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide.

Example 8 2-[5-Amino-6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[l-(2-[5-(α,α-dimethyl-3,4methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide.

Example 9 2-[6-Oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-*(R,S)*-methylpropyl]acetamide.

Example 10 2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide.

Example 11 2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-*(R,S)*-methylpropyl]acetamide.

Example 12 2-[6-Oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-*(R,S)*-methylpropyl]acetamide.

Example 13 2-[5-Methyloxycarbonylamino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(*tert*-butyl)-1,3,4-oxadiazolyl]carbonyl)-2-*(R,S)*-methylpropyl]acetamide.

The compounds of the present invention are not limited to use for inhibition of human elastase. Elastase is a member of the class of enzymes known as serine proteases. This enzyme class also includes, for example, chymotrypsin, cathepsin G, trypsin and thrombin. These proteases have in common a catalytic triad consisting of Serine-195, Histidine-57 and Aspartic acid-102 (chymotrypsin numbering system). The precise hydrogen bond network that exists between these amino acid residues allows the Serine-195 hydroxyl to form a tetrahedral intermediate with the carbonyl of an amide substrate. The decomposition of this intermediate results in the release of a free amine and the acylated enzyme. In a subsequent step, this newly formed ester is hydrolyzed to give the native enzyme and the carboxylic acid. It is this carboxyl component that helps characterize the specificity for the enzyme. In the example in which the carboxyl component is a peptide, the alpha-substituent of the amino acid is predominately responsible for the specificity toward the enzyme. Utilizing the accepted nomenclature by Schechter and Berger *(Biochem. Biophy. Res. Commun.*, 27:157 (1967) and *Biochem. Biophys. Res. Commun.*, 32:898 (1968)), the amino acid residues in the substrate that undergo the cleavage are defined as $P_1 \ldots P_n$ toward the N-terminus and $P_1' \ldots P_n'$ toward the C-terminus. Therefore, the scissile bond is between the P_1 and the P_1' residue of the peptide subunits. A similar nomenclature is utilized for the amino acid residues of the enzyme that make up the binding pockets accommodating the subunits of the substrate, where the binding pocket for the enzyme is designated by $S_1 \ldots S_n$ instead of $P_1 \ldots P_n$ as for the substrate.

The characteristics for the P_1 residue defining serine proteinase specificity is well established. The proteinases may be segregated into three subclasses: elastases, chymases and tryptases based on these differences in the P_1 residues. The elastases prefer small aliphatic moieties such as valine whereas the chymases and tryptases prefer large aromatic hydrophobic and positively charged residues respectively.

One additional proteinase that does not fall into one of these categories is propyl endopeptidase. The P_1 residue defining the specificity is a proline. This enzyme has been implicated in the progression of memory loss in Alzheimer's patients. Inhibitors consisting of α-keto heterocycles have recently been shown to inhibit propyl endopeptidase (Tsutsumi et al., *J. Med. Chem.*, 37, 3492-3502 (1994)). By way of extension, α-keto heterocycles as defined herein allow for an increased binding in P' region of the enzyme.

Table 1. P_1 Characteristics for Proteinase Specificity

Proteinase Class	Representative Enzyme	P_1 Characteristic
Elastases	Human Neutrophil Elastase	small aliphatic residues
Chymases	alpha- Chymotrypsin, Cathepsin G	aromatic or large hydrophobic residues
Tryptases	Thrombin, Trypsin, Urokinase, Plasma Kallikrein, Plasminogen Activator, Plasmin	positively charged residues
Other	Prolyl Endopeptidase	proline

Since the P_1 residue predominately defines the specificity of the substrate, the present invention relates to P_1-P_n' modifications, specifically, certain alpha-substituted keto-heterocycles composed of 1,2,4 oxadiazoles and 1,3,4-oxadiazoles. By altering the alpha-substituent to the ketone and, to some extent, the substituent on the heterocycle, the specificity of these compounds can be directed toward the desired proteinase (e.g., small aliphatic groups for elastase).

The efficacy of the compounds for the treatment of various diseases can be determined by scientific methods, which are known in the art. The following are noted as examples for HNE mediated conditions:

- for acute respiratory distress syndrome, the method according to human neutrophil elastase (HNE) model *(AARD,* 141:227-677 (1990)); the endotoxin induced acute lung injury model in minipigs *(AARD,* 142:782-788 (1990)); or the method according to human

polymorphonuclear elastase-induced lung hemorrhage model in hamsters (European Patent Publication No. 0769498) may be used;

- in ischemia/reperfusion, the method according to the canine model of reperfusion injury (*J. Clin. Invest.*, 81: 624-629 (1988)) may be used.

The compounds of the present invention, salts thereof, and their intermediates can be prepared or manufactured as described herein or by various processes known to be present in the chemical art (see e.g., WO 96/16080).

Alternatively, the compounds of the present invention may be prepared as described in Figures 1, 2 and 3. Figure 1 relates to the synthesis of the Boc protected amino alcohol intermediates used in the invention. Figures 2 and 3 show the use of the intermediates for the synthesis compounds of the invention.

The 2-substituted 1,3,4-oxadiazoles (3) may be prepared via formation of methyl esters from the corresponding acids (1) utilizing, for example, thionyl chloride and methanol, followed by treatment with hydrazine in a suitable solvent to yield hydrazonic acids (2). Alternatively, esters can be prepared by methods known to one skilled in the art or those methods described in Comprehensive Organic Transformations (R. Larock, VCH Publishers 1989, 966-972). Reaction of (2) with triethyl orthoformate or trimethyl orthoformate and TsOH gives the requisite 2-substituted 1,3,4-oxadiazoles (3).

Intermediate (3') can be formed utilizing standard conditions (e.g., butyllithium. or other known alkyl lithium reagents, at low temperature in a polar aprotic solvent, and further, if desired, reacting with $MgBr{\cdot}OEt_2$) and subsequently added to aldehyde (4) to give alcohol (5).

The aldehyde (4) may be prepared via any of three methods as described in Figure 1. One method reduces the intermediate that is formed between Boc-Val-OH and *iso*-propylchloroformate with sodium borohydride to give Boc-Valinol (12). In a subsequent step, the Boc-Valinol is oxidized with SO_3-Py in DMSO to give aldehyde (4). Another such method takes the Weinreb amide (13) that is prepared from Boc-Val-OH (11) and reduces it to the aldehyde using diisobutylaluminum hydride (DIBAL). Alternatively, one may generate the ester (14) of the amino acid followed by reduction with DIBAL to afford aldehyde (4).

As shown in Figures 2 and 3, deprotection of amine (5) using hydrochloric acid in dioxane gives the amino hydrochloride (6), which is then coupled to the desired acid (7) or (7') by methods available to one skilled in the art to give intermediate (8) or (8'). Oxidation using the Swern Oxidation, Dess-Martin's Periodinane or other methods as described in Oxidation in

Organic Chemistry (M. Hudlicky, ACS Monograph 186 (1990)) yields the desired ketone (9) or (9').

Where a compound is substituted at the 5 position of the pyrimidinone group with a benzyloxycarbonylamino group, a deprotection step can be conducted as described in Figure 3. This step requires removal of the protecting group from the amine and may be carried out by a number of methods. For example, one may utilize aluminum chloride, anisole and nitromethane in a suitable solvent such as dichloromethane to give the 5-amino compound (10'). Other methods of deprotection available in the art may also be used.

Although the compounds described herein may be administered as pure chemicals, it is preferable to present the active ingredient as a pharmaceutical composition. The invention thus further provides the use of a pharmaceutical composition comprising one or more compounds together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

Pharmaceutical compositions include those suitable for oral or parenteral (including intramuscular, subcutaneous and intravenous) administration. The compositions may, where appropriate, be conveniently presented in discrete unit dosage forms and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with liquid carriers, solid matrices, semi-solid carriers, finely divided solid carriers or combination thereof, and then, if necessary, shaping the product into the desired delivery system.

Pharmaceutical compositions suitable for oral administration may be presented as discrete unit dosage forms such as hard or soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or as granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art, e.g., with enteric coatings.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may

contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds may also be formulated for parenteral administration (e.g., by injection, for example, bolus injection or continuous infusion) and may be presented in unit dose form in ampules, pre-filled syringes, small bolus infusion containers or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds may be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. Suitable transdermal delivery systems are disclosed, for example, in Fisher et al. (U.S. Patent No. 4,788,603) or Bawas et al. (U.S. Patent No. 4,931,279, 4,668,504 and 4,713,224). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The active ingredient can also be delivered via iontophoresis, e.g., as disclosed in U.S. Patent Nos. 4,140,122, 4,383,529, or 4,051,842.

Compositions suitable for topical administration in the mouth include unit dosage forms such as lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; mucoadherent gels, and mouthwashes comprising the active ingredient in a suitable liquid carrier.

When desired, the above-described compositions can be adapted to provide sustained release of the active ingredient employed, e.g., by combination thereof with certain hydrophilic polymer matrices, e.g., comprising natural gels, synthetic polymer gels or mixtures thereof.

The pharmaceutical compositions according to the invention may also contain other adjuvants such as flavorings, coloring, antimicrobial agents, or preservatives.

It will be further appreciated that the amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and

the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg/day, e.g., from about 1 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

The compound is conveniently administered in unit dosage form, for example, containing 0.5 to 1000 mg, conveniently 5 to 750 mg, and most conveniently, 10 to 500 mg of active ingredient per unit dosage form.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μM, more preferably, about 1 to 50 μM, and most preferably, about 2 to about 30 μM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 0.5-500 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

The desired dose may be conveniently presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations, such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

The following examples are given to illustrate the invention and are not intended to be inclusive in any manner.

Examples

The compounds of the present invention, salts thereof, and their intermediates can be prepared or manufactured as described herein or by various processes known to be present in the chemical art. By way of an example, the final step in the process defined here, is an oxidation of a 2° alcohol to a ketone. As described here, this transformation from an alcohol to ketone was preformed using dimethylsulfoxide and oxalyl chloride followed by base, which is known as the Swern oxidation. However, modifications of the Swern oxidation are known in the art and are acceptable in this present invention. It is known that alternative electrophilic molecules can be substituted for oxalyl chloride such as dicyclohexylcarbodiimide, acetic anhydride, trifluoroacetic anhydride or sulfur trioxide (Mancuso et al., Synthesis 165 (1981)). Alternatively, other oxidative methods can be used such as N-chlorosuccinimide (NCS) followed by base as described by the inventors in U.S. Pat. No. 5,618,792 or periodinane such as the Dess-Martin reagent. Still other methods may also be appropriate as described in Oxidation in Organic Chemistry (M. Hudlicky, ACS Monograph 186 (1990)).

Besides the methods described below, other methods can be used for making substituted oxadiazole nonpeptides. U.S. Patent 5,807,829, incorporated herein by reference, teaches some other methods for making substituted oxadiazole nonpeptides.

The skilled artisan will understand that where a particular enantiomer is mentioned, the mirror-image enantiomer or a mixture of enantiomers can be used.

Symbols have the standard meanings as familiar to one skilled in the art, by way of example the following have been used: ml (milliliters), g (grams), TLC (thin layer chromatography), R_f (the ratio of the distance moved by a compound to the distance that the solvent front moved during the same time on a TLC plate), ^1H NMR (proton nuclear magnetic resonance), DMSO-d6 (deuterodimethylsulfoxide) and $CDCl_3$ (deuterochloroform).

Example 1 Methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(*tert*-butyl)-oxadiazolyl]carbonyl)-2-*(S)*-methylpropyl]-*L*-prolinamide.

The secondary alcohol, methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(*tert*-butyl)-oxadiazolyl] hydroxymethyl)-2-*(S)*-methylpropyl]-*L*-prolinamide, was oxidized using one of the methods known to one skilled in the art, such as, the Swern Oxidation. The intermediate methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(*tert*-butyl)-oxadiazolyl] hydroxymethyl)-2-*(S)*-methylpropyl]-*L*-prolinamide was prepared as follows:

A. *tert*-Butylcarbohydrazonic acid

The mixture of methyl trimethylacetate (230 ml) and hydrazine monohydrate (170 ml) was refluxed for 24 hours. The reaction was cooled to room temperature, and concentrated

under reduced pressure. The residue was azeotroped with toluene several times, dissolved in a saturated aqueous solution of sodium chloride, and extracted with chloroform (4x). The extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give *tert*-butylcarbohydrazonic acid (176 g) having the following physical data.

TLC: R_f= 0.59, chloroform: methanol (10:1).

^{1}H NMR (DMSO-d_6): δ8.78 (1H, brs), 4.15 (2H, brs), 1.08 (9H, s).

B. 2-*tert*-Butyl-1,3,4-oxadiazole

The mixture consisting of *tert*-butylcarbohydrazonic acid (176 g), trimethyl orthoformate (250 ml) and p-toluenesulfonic acid monohydrate (4.3 g) was heated and methanol removed by distillation at a temperature ranging from 90°C to 110°C. Trimethyl orthoformate was removed (50°C/43 mm Hg) and the residue was distilled at 120°C/23 mm Hg to give 2-*tert*-Butyl-1,3,4-oxadiazole (131 g) having the following physical data.

TLC: R_f= 0.68, chloroform: methanol (10:1).

^{1}H NMR (DMSO-d_6): δ9.12(l H,s), 1.3 6 (9H, s).

C. 1-[2-(5-*tert*-Butyl)-1,3,4-oxadiazolyl]-2-*(S)*-(*tert*-butoxycarbonylamino)-3-methylbutan-1-ol

To a solution of 2-*tert*-Butyl-1,3,4-oxadiazole (62.1 g) in tetrahydrofuran (1650 ml) was added *n*-butyllithium in hexane (1.6 M, 307.8 ml) dropwise at -78°C under an atmosphere of argon. The mixture was stirred for 40 min at -78°C, magnesium bromide diethyl etherate (127.2 g) was added, and the resulting mixture was allowed to warm to -45°C. After 1.5 hours, a solution of 2-(S)-[N-(*tert*-butoxycarbonyl)amino]-3-methylbutanal (90 g) in tetrahydrofuran (60 ml) was added dropwise at -45°C and allowed to warm to -15°C. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, and extracted with ethyl acetate. The extract was washed with water (x3) and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck 7734) (ethyl acetate:hexane = 1:20 to 1:1) to give 1-[2-(5-*tert*-butyl)-1,3,4-oxadiazolyl]-2-*(S)*-(*tert*-butoxycarbonylamino)-3-methylbutan-1-ol (78.6 g) having the following physical data.

TLC: R_f = 0.42, hexane:ethyl acetate (1:1).

^{1}H NMR ($CDCl_3$): δ5.16-4.90 (2H, m), 4.67 (1H, m), 4.23 (1H, m), 3.90 (1H, m), 3.66 (1H, m), 1.98 (1H, m), 1.42, 1.41 and 1.36 (total 18H, each s), 1.13-0.90 (6H, m).

D. 1-[2-(5-*tert*-Butyl)-1,3,4-oxadiazolyl]-2-*(S)*-amino-3-methylbutan-1-ol Hydrochloride

To a solution of 1-[2-(5-*tert*-butyl)-1,3,4-oxadiazolyl]-2-*(S)*-(*tert*-butoxycarbonylamino)-3-methylbutan-1-ol (76.3 g) in dioxane (200 ml) was added 4N hydrochloric acid in dioxane solution (1000 ml) at 0°C. The reaction mixture was concentrated under reduced pressure. The residue was solidified with diethyl ether. The solid was azeotroped with benzene several times to give 1-[2-(5-*tert*-butyl)-1,3,4-oxadiazolyl]-2-*(S)*-amino-3-methylbutan-1-ol hydrochloride (66.1 g) having the following physical data.

TLC: $R_f = 0.30$, chloroform:methanol (10:1);

^{1}H NMR ($CDCl_3$): δ8.50-8.10 (2H, br), 7.10-6.80 (1H, br), 5.55-5.35 (1H, m),3.95-3.60 (2H, m), 2.10 (1H, m), 1.41 (9H, s), 1.20-1.00 (6H, m).

E. Methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(*tert*-butyl)-oxadiazolyl]hydroxymethyl)-2-*(S)*-methylpropyl]-*L*-prolinamide

Prepared using methyloxycarbonyl-*L*-Val-Pro-OH and 1-[2-(5-*tert*-Butyl)-1,3,4-oxadiazolyl]-2-*(S)*-amino-3-methylbutan-1-ol hydrochloride and a coupling method know to one skilled in the art.

The product had the following physical data.

TLC: $R_f = 0.58$, ethyl acetate.

^{1}H NMR: (200 MHz, $CDCl_3$), δ 7.53 (brd., J= 6.2 Hz, 1H, NH), δ 5.45-5.29 (m 2H, NH, and α CH of P_1 Val), δ 4.79-4.62 (m, 1H, α CH of Pro), 4.32 (m, 1H, α CH of P_3-Val), 3.83-3.51 (m, 2H, NCH_2 of Pro), 3.68 (s, 3H, CH_3O), 2.55-1.80 (m, 6H, CHs of *iso*-Pr, and CH_2CH_2 of Pro), 1.47 (s, 9H, CH_3s of *t*-Bu), 1.16-0.86 (m, 12H, CH_3s of *iso*-Pr).

Example 2 Methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(α,α-dimethylbenzyl)-oxadiazolyl]carbonyl)-2-*(S)*-methylpropyl]-*L*-prolinamide

The compound was prepared by oxidizing methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(α,α-dimethylbenzyl)-oxadiazolyl]hydroxymethyl)-2-*(S)*-methylpropyl]-*L*-prolinamide using a procedure know to one skilled in the art, such as, the Swern Oxidation.

The intermediate, methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(α,α-dimethylbenzyl)-oxadiazolyl]hydroxymethyl)-2-*(S)*-methylpropyl]-*L*-prolinamide, was prepared using methyloxycarbonyl-*L*-Val-Pro-OH and 1-[2-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]-2-*(S)*-amino-3-methylbutan-1-ol hydrochloride and a coupling method know to one skilled in the art. The intermediate 1-[2-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]-2-*(S)*-amino-3-methylbutan-1-ol hydrochloride was prepared using a similar procedure as described in Example 1 except methyl phenylisobutyrate was used instead of methyl trimethylacetate.

The product had the following physical data.

TLC: R_f = 0.64, ethyl acetate.

1H NMR (200 MHz, $CDCl_3$): 7.84 and 7.49 (each brd., J=7.6 Hz, totally 1H, NH), 7.40-7.20 (m, 5H aromatic Hs), 5.46-5.29 (m, 2H, NH and α CH of P_1 Val), 4.77-4.60 (m, 1H, α CH of Pro), 4.40-4.25 (m, 1H α CH of P_3 Val), 3.84-3.55 (m, 2H, NCH_2 of Pro), 3.68 (s, 3H, CH_3O), 2.55-1.76 (m, 6H, CHs of *iso*-Pr andCH_2CH_2 of Pro), 1.88 (s, 6H, het$C(CH_3)_2Ph$), 1.12-0.82 (m, 12H, CH_3s of *iso*-Pr).

Example 3 Methyloxycarbonyl-*L*-valyl-*N*-[1 -(2-[5-(α,α-dimethyl-3,4-methylene-dioxybenzyl)- 1,3,4-oxadiazolyl]carbonyl)-2-*(S)*-methylpropyl]-L-prolinamide

The compound was prepared by oxidizing methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-oxadiazolyl]hydroxymethyl)-2-*(S)*-methylpropyl]-*L*-prolinamide using a procedure know to one skilled in the art, such as, the Swern Oxidation.

The intermediate, methyloxycarbonyl-*L*-valyl-*N*-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-oxadiazolyl]hydroxymethyl)-2-*(S)*-methylpropyl]-*L*-prolinamide, was prepared using methyloxycarbonyl-*L*-Val-Pro-OH and 1-[2-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]-2-*(S)*-amino-3-methylbutan-1-ol hydrochloride and a coupling method know to one skilled in the art. The intermediate 1-[2-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]-2-*(S)*-amino-3-methylbutan-1-ol hydrochloride was prepared using a similar procedure as described in Example 1 except methyl 3,4-methylenedioxyphenylisobutyrate was used instead of methyl trimethylacetate.

The product had the following physical data.

TLC: Rf = 0.63, ethyl acetate.

^{1}H NMR (200 MHz, $CDCl_3$): 7.49 (d, J=6.4 Hz, 1H, NH), 6.85-6.73 (m, 3H, aromatic Hs), 5.95 (s, 2H, OCH_2O), 5.46-5.28 (m, 1H α CH of Pro), 4.30 (m, 1H, α CH of P_3-Val), 3.84-3.54 (m, 2H, NCH_2 of Pro), 3.68 (s, 3H, CH_3O), 2.55-1.78 (m, 6H, CHs of *iso*-Pr, and CH_2CH_2 of Pro), 1.83 (s, 6H, HetC(CH_3)2Ph), 1.11-0.85 (m, 12H, CH_3s of *iso*-Pr).

Example 4 2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-*tert*-butyl-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyllacetamide

To a solution of oxalyl chloride (5.80 ml) in dichloromethane (160 ml) was slowly added dropwise a solution of dimethylsulfoxide (9.44 ml) in dichloromethane (16 ml) at –78°C under an atmosphere of argon. The mixture was stirred for 30 min at 78°C. To the mixture was added dropwise a solution of 2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-

[1-(2-[5-*tert*-butyl-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyl]acetamide (15.2g) in dichloromethane (160 ml) at –78°C. The mixture was stirred for 2 hours at –78°C. To the resulting solution was added triethylamine (97.2 ml) dropwise at –78°C. The reaction mixture was warmed up to room temperature, and stirred for 34 hours at the same temperature. The reaction mixture was acidified by addition of 2N aqueous solution of hydrochloric acid, and extracted with dichloromethane. The extract was washed with 2N aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel using a gradient elution of 66 to 100% ethyl acetate/hexane to give 2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-*tert*-butyl-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide (10.92 g) having the following physical data.

TLC: R_f = 0.63, chloroform:methanol (10:1).

^{1}H NMR ($CDCl_3$): δ 8.00(1H, d, J=6.5 Hz), 7.64 (2H, dd, J=8.6, 5.4 Hz), 7.17 (2H, t, J=8.6 Hz), 6.95 (IH, brd, J=8.4 Hz), 6.50 (IH, d, J=6.5 Hz), 5.43 (IH, dd, J=8.4, 4.8 Hz), 4.63 and 4.58 (each 1H, each d, J=15.4 Hz), 2.53 (IH, m), 1.48 (9H, s), 1.09 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz).

The intermediate 2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-*tert*-butyl-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyl]acetamide was prepared as follows:

A. *tert*-Butylcarbohydrazonic acid

t-Butylcarbohydrazonic acid was prepared as described above.

TLC: R_f=0.59,chloroform:methanol (10:1).

^{1}H NMR (DMSO-d_6): δ 8.78 (1 H, brs), 4.15 (2H,brs), 1.08 (9H, s).

B. 2-*tert*-Butyl 1,3,4-oxadiazole

t-*tert*-Butyl 1,3,4-oxadizole was prepared as described above.

C. 1-[2-(5-*tert*-Butyl)-1,3,4-oxadiazolyl]-2-(*S*)-(*tert*-butoxycarbonylamino)-3-methylbutan-1-ol

To a solution of 2-*tert*-Butyl-1,3,4-oxadiazole (62.1 g) in tetrahydrofuran (1650 ml) was added *n*-butyllithium in hexane (1.6 M, 307.8 ml) dropwise at –78°C under an atmosphere of argon. The mixture was stirred for 40 min at –78°C , magnesium bromide diethyl etherate (127.2 g) was added, and the resulting mixture was allowed to warm to –45°C.

After 1.5 hours, a solution of 2-(S)-[N-(*tert*-butoxycarbonyl)amino]-3-methylbutanal (9O g) in tetrahydrofuran (60 ml) was added dropwise at −45°C and allowed to warm to −15°C. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, and extracted with ethyl acetate. The extract was washed with water (x3) and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck 7734) (ethyl acetate:hexane = 1:2O → 1:1)

to give 1-[2-(5-*tert*-butyl)-1,3,4-oxadiazolyl]-2-(*S*)-(*tert*-butoxycarbonylamino)-3-methylbutan-1-ol (78.6 g) having the following physical data.

TLC: R_f = 0.42, hexane:ethyl acetate (1:1).

^{1}H NMR ($CDCl_3$): δ 5.16-4.90 (2H, m), 4.67 (1H, m), 4.23 (1H, m), 3.90 (1H, m), 3.66 (1H, m), 1.98 (1H, m), 1.42, 1.41 and 1.36 (total 18H, each s), 1.13-0.90 (6H, m).

D. 1-[2-(5-*tert*-Butyl)-1,3,4-oxadiazolyl]-2-(*S*)-amino-3-methylbutan-1-o1 Hydrochloride

To a solution of 1-[2-(5-*tert*-butyl)-1,3,4-oxadiazolyl]-2-(*S*)-(*tert*-butoxycarbonylamino)-3-methylbutan 1-ol (76.3 g) in dioxane (200ml) was added 4N hydrochloric acid in dioxane solution (1000 ml) at 0°C. The reaction mixture was concentrated under reduced pressure. The residue was solidified with diethyl ether. The solid was azeotroped with benzene several times to give l-[2-(5-*tert*-butyl)-l,3,4-oxadiazolyl]-2-(S)-ainino-3-methylbutan-1-ol hydrochloride (66.1 g) having the following physical data.

TLC: R_f= 0.30, chloroform:methanol (10:1);

^{1}H NMR ($CDCl_3$): δ 8.50-8.10 (2H, br), 7.10-6.80 (1 H, br), 5.55-5.35 (1H, m), 3.95-3.60 (2H, m), 2.10 (1H, m), 1.41 (9H, s), 1.20-1.00 (6H, m).

E. 2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-*tert*-butyl-1,3,4-oxadiazol]hydroxymethyl-)2-(*S*)-methylpropyl]acetamide

To a solution of 1-[2-(5-*tert*-butyl)-1,3,4-oxadiazolyl]-2-(*S*)-amino-3-methylbutan-1-ol hydrochloride (10.76 g), [6-oxo-2-(4flurophenyl)-1,6-dihydro-1-pyrimidinyl]acetic acid (8.63 g) and 1-hydroxybenzotriazole (5.85 g) in dimethylformamide (100 ml) was added 1-ethyl-3-[3-(dimethylamino) propyl]carbodiimide (7.33 g) at 0°C. To the resulting mixture was added 4-methylmorpholine (4.21 ml) at the same temperature. The reaction mixture was stirred for 17 hours at room temperature. The reaction was quenched by addition of water, extracted with ethyl acetate (x3). The extract was washed with aqueous 10% citric acid solution, a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium

sulfate and concentrated under reduced pressure to 2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-tertbutyl1,3,4-oxadiazolyl]hydroxymethyl)-2-(S)-methylpropyl]acetarnide (14.6 g) having the following physical data.

TLC: R_f = 0.40, chloroform:methanol (10:1);

^{1}H NMR (DMSO-d_6): δ 8.00 and 7.94 (each 1H, each d, J=6.6Hz), 7.71 and 7.55 (each 2H, each m), 7.19 and 7.18 (each 2H, each J=6.6Hz), 6.43 and 6.3 8 (each 1H, each d, J=6.6Hz), 5.13 (1H, d, J=2.2Hz), 5.05 (1H, d, J=4.4Hz), 4.54 (2H, s), 4.43 (2H, m), 4.31 (1H, m), 4.04 (lH, m), 2.20-1.52 (1H, m), 1.41 and 1.37 (each 9H, each s), 1.08, 1.00, 0.94 and 0.92 (each 3H, each d, J=6.6Hz).

Example 5 2-[5-Benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[l-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide

The compound was prepared using a similar oxidative procedure as described in Example 1 utilizing 2-[5-benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyl]acetamide for the 2° alcohol. The title compound, 2-[5-benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide, gave the following physical data.

TLC: R_f= 0.66, chloroform:methanol (10:1);

^{1}H NMR ($CDC1_3$): δ 8.76 (1H, brs), 7.63-7.52 (2H, m), 7.49 (1H, brs), 7.38 (5H, brs), 7.13 (2H, t, J=8.6Hz), 6.82-6.74 (3H, m), 6.71 (1 H, brd, J=8.6Hz), 5.94 (2H, s), 5.42 (1H, dd, J=8.6, 5.0Hz), 5.22 (2H, s), 4.58 (2H, brs), 2.50 (1H, m), 1.83 (6H, s), 1.05 and 0.86 (each 3H, each d, J=7.OHz).

The intermediate 2-[5-benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyl]acetamide was prepared in an analoguous manner as described in Example 1 E using [5-benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]acetic acid and 1-[2(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]-2-(*S*)-amino-3-methylbutan-l-o1 hydrochloride. The intermediate 1-[2-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]-2-(*S*)-amino-3-methylbutan-l-ol hydrochloride was prepared using a similar procedure as described in

Example 1 D. The heterocyclic intermediate 2-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazole gave the following physical data.

TLC: R_f = 0.69, chloroform:methanol (10:1).

^{1}H NMR ($CDCl_3$): δ 8.30 (1H, s), 6.78(1H, brs), 6.74(2H, brs), 5.94 (2H, s), 1.81 (6H, s).

Example 6 2-[5Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide

To 2-[5-(benzyloxycarbonylamino)-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide (1.42 g) was added 30% hydrobromic acid in acetic acid solution (50 ml). The reaction mixture was stirred for I hour at room temperature. The reaction mixture was quenched by addition of ice water, extracted with ethyl acetate (x2). The combined extracts were washed with water (x2) and a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a gradient elution of 50 to 100% ethyl acetate/hexane to give 2-[5-amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1- pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide (457 mg) having the following physical data.

TLC: R_f= 0.39, ethyl acetate.

^{1}H NMR ($CDCl_3$): δ 7.53 (2H, dd, J=8.8, 5.3Hz), 7.48 (1H, s), 7.06 (2H, t, J=8.8Hz), 6.90 (1H, brd, J=8.4Hz), 6.84-6.70 (3H, m), 5.95 (2H, s), 5.43 (1H, dd, J=8.4, 4.8 Hz), 4.63 and 4.54 (each 1H Abq, J=15.0Hz), 4.05 ((2H, brs), 2.51 (1H, m), 1.84 (6H, s), 1.06 and 0.87 (each 3H, each d, J=7.0Hz).

Example 7 2-[5-Benzyloxycarbonylamino-6-oxo-2-pheny-l-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide

The compound was prepared using a similar oxidative procedure as described in Example 1 utilizing 2-[5-benzyloxycarbonylamino-6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[l-(2-[-5(α,α-dimethyl-3,4methylenedioxybenzyl)-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyljacetamide for the 2° alcohol. The title compound, 2-[5-benzyloxycarbonylamino-6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-

methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide gave the following physical data.

TLC: R_f= 0.34, hexane:ethyl acetate (1:1).

^{1}H NMR ($CDCl_3$): δ 8.78 1H, brs), 7.60-7.30 (1H, m), 6.78 (3H, m), 6.68 (1H, d, J=8.8Hz), 5.94 (2H, s), 5.42 (1H, dd, J=8.8, 4.8Hz), 5.23 (2H, s), 4.65 and 4.57 (2H, Abq, J=15.0Hz), 2.49 (IH, m), 1.83 (6H, s), 1.04 (3H, d, J=6.Hz), 0.84 (3H, d, J=5.8Hz).

The intermediate 2-[5-benzyloxycarbonylamino-6-oxo-2phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyl]acetamide was prepared in an analogous manner as described in Example 1 E using 5-benzyloxycarbonylamino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]acetic acid and 1-[2-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]-2-(*S*)-amino-3-methylbutan-l-o1 hydrochloride. The intermediate 1-[2-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]-2-(*S*)-amino-3-methylbutan-l-o1 hydrochloride was prepared using a similar procedure as described in Example 1 D. The heterocyclic intermediate 2-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazole gave the following physical data.

TLC: R_f = 0. 69, chloroform: methanol (10:1).

^{1}H NMR ($CDCl_3$): δ 8.30 (1H, s), 6.78(1H, brs), 6.74(2H, brs), 5.94 (2H, s), 1.81 (6H, s).

Example 8 2-[5-Amino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide

The compound was prepared using a similar procedure as described in Example 3 utilizing 2-[5-benzyloxycarbonylamino-6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5(-α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide. The title compound 2-[5-Amino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide gave the following physical data.

TLC: R_f = 0.40, ethyl acetate.

^{1}H NMR ($CDCl_3$): δ 7.59-7.34 (5H, m), 7.50 (1H, s), 6.86 (1H, d, J=8.2Hz), 6.86-6.72 (3H, m), 5.95 (2H, s), 5.43 (1H, dd, J=8.2 and 4.8Hz), 4.66 1H, d, J=15.4Hz), 4.56 (2H, f, J=15.4hz), 4.05 (2h, brs), 2.62-2.36 (1H, m), 1.84 (6H, s), 1.05(3H, d, J=7.0Hz), 0.85 (3H, d, J=7.0Hz).

Example 9 2-[6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyllcarbonyl)-2-(*R,S*)-methylpropyl] acetamide

TLC: R_f = 0.46, ethyl acetate.

^{1}H NMR ($CDCl_3$): δ 8.01 (1H, d, J=6.6Hz), 7.65-7.35 (5H, m), 6.87 (1H, d, J=8.6,Hz), 6.85-6.70 (3H, m), 6.49 (1H, d, J=6.6Hz), 5.95 (2H, s), 5.42 (1H, dd, J=8.6 and 5.0Hz), 4.67 (1H, d, J=15.2Hz), 4.54 (1H, d, J=15.2Hz), 2.63-2.37 (1H, m), 1.84 (6H, s), 1.05 (3H, d, J=6.8Hz), 0.85 (3H, d, J=6.8Hz)

Example 10 2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl] acetamide

TLC: R_f = 0.43, ethyl acetate.

^{1}H NMR ($CDCl_3$): δ 7.99 (1H, d, J=6.6Hz), 7.63 (2h, dd, J=8.6, 5.2Hz), 7.14 (2H, t, J=8.6Hz), 6.93 (1H, brd, J=8.6Hz), 6.84-6.70 (3H, m), 6.49 (1H, d, J=6.6Hz), 5.95 (2H, s), 5.41 (1H, dd, J=8.6, 5.0Hz), 4.64 and 4.53 (each 1H, Abq, J= I 5.0Hz), 2.50 (1H, m), 1.84 (6H, s), 1.06 and 0.87 (each 3H, each d, J=7.0Hz).

Example 11 2-[6-oxo-2-(4-fluorophenyl-)1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)methylpropyl]acetamide

The compound was prepared using a similar oxidative procedure as described in Example 1 utilizing 2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyl]acetamide for the 2° alcohol. The title compound, 2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide, gave the following physical data.

TLC: R_f = 0.42, ethyl acetate.

^{1}H NMR ($CDCl_3$): δ 7.99 (1H, d, J=6.5Hz), 7.62 (2H, m), 7.40-7.20 (5H, m), 7.14 (2H, t, J=8.8Hz), 6.89 (1H, brd, J=8.6Hz), 6.49 (1H, d, J=6.5Hz), 5.42 (1H, dd, J=8.6, 5.0Hz), 4.61 and 4.54 (each 1H, each d, J=15.0Hz), 2.50 (1H, m), 1.88 (6H, s), 1.06 and 0.86 (each 3H, each d, J=6.7Hz).

The intermediate 2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyl]acetamide was prepared in an analoguous manner as described in Example 1 E using [6-oxo-2-(4-fluorophenyl)1,6-dihydro-1-pyrimidinyllacetic acid and 1-[2-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]-2-

(*S*)-amino-3-methylbutan-l-ol hydrochloride. The intermediate 1-[2-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]-2-(*S*)-amino-3-methylbutan-1-ol hydrocloride was prepared using a similar procedure as described in Example 1 D. The heterocyclic intermediate 2-(α,α-dimethylbenzyl)-l,3,4-oxadiazole gave the following physical data.

TLC: R_f= 0.43, ethyl acetate:hexane (1:2).

^{1}H NMR ($CDCl_3$): δ 8.31 (1H, s), 7.40-7.14 (5H, m), 1.86 (6H, s).

Example 12 2-[6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide

The compound was prepared using a similar oxidative procedure as described in Example 4 utilizing 2-[6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyflacetamide for the 2° alcohol. The title compound, 2-[6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]atetamide, gave the following physical data.

TLC: R_f = 0.44, ethyl acetate.

^{1}H NMR ($CDCl_3$): δ 8.02 (1H, d, J=6.5Hz), 7.64-7.24 (10H, m), 6.82 (1H, brd, J=8.4Hz), 6.50 (1H, d, J=6.5Hz), 5.44 (1H, dd, J=8.4, 4.8Hz), 4.63 and 4.56 (each 1H, each d, J=15.4Hz), 2.50 (1H, m), 1.89 (6H, s), 1.06 and 0.86 (each 3H, each d, J=6.8Hz).

The intermediate 2-[6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]hydroxymethyl)-2-(*S*)-methylpropyl]acetamide was prepared in an analoguous manner as described in Example 1 E using [6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]acetic acid and 1-[2-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]-2-(*S*)-amino-3-methylbutan-l-ol hydrochloride.

Example 13 2-[5-Methyloxycarbonylamino-6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(*tert*-butyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)methylpropyl]acetamide.

Prepared by a procedure analogous to that of Example 7. The product had the following physical data.

TLC: Rf = 0.57 methanol:chloroform, 1:10.

^{1}H NMR (200 MHz, $CDCl_3$): 8.78 (brs, 1H, H of pyrimidinone), 7.62-7.40 (m, 6H, NH and aromatic Hs), 6.73 (brd, J=8.4 Hz, 1H, CONH), 5.45 (dd, J=8.4, 5.0 Hz, 1H, α CH of Val), 4.67 and 4.61 (each d, J=15.0 Hz, each 1H, CH_2 of Gly), 3.81 (s, 3H, CH_3O), 2.51 (m,

1H, CH of *iso*-Pr), 1.48 (s, 9H, CH_3s of *t*-Bu), 1.07 and 0.88 (each d, J=6.8 Hz, each 3H, CH3s of *iso*-Pr).

Example 14 — In Vitro Inhibition of Elastase

The following protocol was used to determine inhibitory activity of compounds described herein. The elastase used in the protocol was derived from human sputum (HSE). A mother solution of the HSE enzyme was prepared from commercially available HSE (875 U/mg protein, SE-563, Elastin Product Co., Inc, Missouri, USA) by diluting with saline to 1,000 U/ml, which was further diluted to 2 U/ml at 0°C prior to use.

A solution was prepared by mixing 100 µl 0.2 M HEPES-NaOH buffer (pH 8.0), 40 µl 2.5 M NaCl, 20 µl 1% polyethyleneglycol 6000, 8 µl distilled water, 10 µl of a DMSO solution of inhibitor and 2 µl solution of N-methoxysuccinyl-Ala-Ala-Pro-Val-p-nitroaniline (at concentrations of 100, 200 and 400 µM). The solution was incubated for 10 minutes at 37°C. To this was added an enzyme solution of HSE (elastase derived from human sputum). The resulting mixture was subjected to the following rate assay.

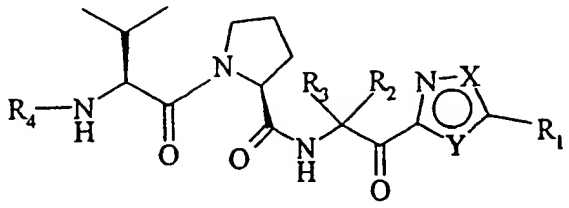
Optical density (SPECTRA MAX 250, Molecular Devices) at 405 nm due to p-nitroaniline generated by the enzyme reaction was measured at 37°C in order to measure the reaction rate during the period that the production rate of p-nitroaniline remains linear. The rate, mO.D./min., was measured for 10 minutes at 30 second intervals immediately after the addition of the enzyme solution. IC_{50} values were determined by log-logit method and converted to K_I values by Dixson plot method. The compounds are presented in Table 2 showing the inhibition activity (K_I values, nM) against HNE.

Table 2. Biological Activity

Example	Name	K_I (nM)
1	Methyloxycarbonyl-*L*-valyl-N-[1-(2-[5-(*tert*-butyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]-*L*-prolinamide	3.0
2	Methyloxycarbonyl-L-valyl-N-[1-(2-[5-(α,αdimethylbenzyl)oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide.	1.32
3	Methyloxycarbonyl-*L*-valyl-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]-*L*-prolinamide.	0.24
4	2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-*tert*-butyl-1,3,4-oxadiazolyllcarbonyl-2-(*R,S*)-methylpropyl]acetamide	44.4
6	2-[5-Amino-6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl-2-(*R,S*)-methylpropyl]acetamide	0.51
8	2-[5-Amino-6-Oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl-2-(*R,S*)-methylpropyl]acetamide	1.06
9	2-[6-Oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl-2-(*R,S*)-methylpropyl]acetamide	0.34
10	2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl-2-(*R,S*)-methylpropyl]acetamide	1.53
11	2-[6-Oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyflacetamide	5.34
12	2-[6-Oxo-2-phenyl-1,6-dihydro-1- pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide	1.83

We claim:

1. A compound of the formula



wherein

X and Y are independently O or N;

R_1 is a,a-dialkylalkylaryl or a,a-dialkylalkyl fused aryl-cycloalkyl wherein the cycloalkyl group is optionally substituted with two or more O atoms;

R_2 and R_3 are independently H or alkyl; or together form a cycloalkyl ring consisting of 3-5 carbons in which one or more carbon atoms of the ring is optionally replaced with a heteroatom selected from O, S or N wherein N is optionally substituted with H or alkyl; and

R_4 is alkyloxycarbonyl;

with the proviso that, if X is O and Y is N, then R_1 is not α,α-dialkylalkylaryl.

2. The compound of claim 1 wherein X is N and Y is O.

3. The compound of claim 2 wherein R_4 is methyloxycarbonyl.

4. The compound of claim 3 wherein R_2 is isopropyl and R_3 is H.

5. The compound of claim 4 wherein R_1 is alkyl.

6. The compound of claim 4 wherein R_1 is a,a-dialkylalkylaryl.

7. The compound of claim 4 wherein R_1 is α,α-dialkylalkyl fused aryl-cycloalkyl wherein the cycloalkyl group is substituted with two O atoms.

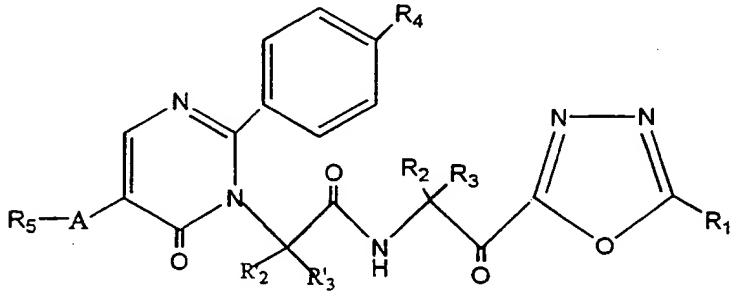
8. A method of inhibiting at least one serine protease comprising administering to a host in need of such inhibition an effective amount of a compound of claim 1.

9. The method of claim 8 wherein the serine protease is elastase.

10. The method of claim 9 wherein the elastase is human neutrophil elastase.

11. A composition comprising one or more compounds of claim 1 and a pharmaceutically acceptable carrier.

12. A compound of the formula



wherein

X and Y are independently O or N;

R_1 is alkyl, α,α-dialkylalkylaryl or α,α-dialkylalkyl fused aryl-cycloalkyl wherein the cycloalkyl group is optionally substituted with two or more O atoms;

R_2 and R_3 are independently H or alkyl; or together form a cycloalkyl ring consisting of 3-5 carbons in which one or more carbon atoms of the ring is optionally replaced with a heteroatom selected from O, S or N wherein N is optionally substituted with H or alkyl;

R'_2 and R'_3 are independently H or alkyl; or together form a cycloalkyl ring consisting of 3-5 carbons in which one or more carbon atoms of the ring is optionally replaced with a heteroatom selected from O, S or N wherein N is optionally substituted with H or alkyl;

A is a direct bond, -NH- or, if R_1 is other than alkyl, -OC(O)-NH-;

R_4 is H or halo; and

R_5 is H, arylalkyl or arylalkyl other than benzyl; or

a pharmaceutically acceptable salt thereof.

13. The compound of claim 12 wherein X is N and Y is O.

14. The compound of claim 13 wherein R_5-A- is H, $-NH_2$, benzyloxycarbonylamino or methyloxycarbonylamino.

15. The compound of claim 14 wherein R_2 is isopropyl and R_3 is H.

16. The compound of claim 15 wherein R_1, is alkyl.

17. The compound of claim 16 wherein R_1 is *tert*-butyl and R_5-A- is selected from H, $-NH_2$, and benzyloxycarbonylamino.

18. A compound of claim 17 selected from:

2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-*tert*-butyl-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide;

2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-*tert*-butyl-1,3,4-oxadiazolyl]carbonyl)-2-(*R*)-methylpropyl]acetamide; or

2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-*tert*-butyl-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide.

19. The compound of claim 15 wherein R_1 is α,α-dialkylalkyl fused aryl-cycloalkyl wherein the cycloalkyl group is substituted with two O atoms.

20. The compound of claim 19 wherein R_1 is α,α-dimethyl-3,4-methylenedioxybenzyl and R_5-A- is selected from H, $-NH_2$, and benzyloxycarbonylamino.

21. A compound of claim 20 selected from:

2-[5-(Benzyloxycarbonyl)amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[l-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide;

2-[5-(Benzyloxycarbonyl)amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[l-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R*)-methylpropyl]acetamide; or

2-[5-(Benzyloxycarbonyl)amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[l-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide.

22. A compound of claim 20 selected from:

2-[5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[l-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide;

2-[5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[l-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R*)-methylpropyl]acetamide; or

2-[5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[l-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide.

23. A compound of claim 20 selected from:

2-[5-(Benzyloxycarbonyl)amino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1 -(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide;

2-[5-(Benzyloxycarbonyl)amino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1 -(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R*)-methylpropyl]acetamide; or

2-[5-(Benzyloxycarbonyl)amino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1 -(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide.

24. A compound of claim 20 selected from:

2-[5-Amino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide;

2-[5-Amino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R*)-methylpropyl]acetamide; or

2-[5-Amino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide.

25. A compound of claim 20 selected from:

2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1 -(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide;

2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1 -(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R*)-methylpropyl]acetamide;

2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1 -(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide.

26. A compound of claim 20 selected from:

2-[6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide;

2-[6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R*)-methylpropyl]acetamide; or

2-[6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethyl-3,4-methylenedioxybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide.

27. The compound of claim 15 wherein R_1 is α,α-dialkylalkylaryl.

28. The compound of claim 27 wherein R_1 is α,α-dimethylbenyzl.

29. A compound of claim 28 selected from:

2-[6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R,S*)-methylpropyl]acetamide;

2-[6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*R*)-methylpropyl]acetamide; or

2-[6-oxo-2-phenyl-1,6-dihydro-l-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(*S*)-methylpropyl]acetamide.

30. A compound of claim 28 selected from:

2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl-2-(*R,S*)-methylpropyl]acetamide;

2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl-2-(*R*)-methylpropyl]acetamide; or

2-[6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-[5-(α,α-dimethylbenzyl)-1,3,4-oxadiazolyl]carbonyl-2-(*S*)-methylpropyl]acetamide.

31. A method of inhibiting at least one serine protease comprising administering to a host in need of such inhibition an effective amount of a compound of claim 12.

32. The method of claim 31 wherein the serine protease is elastase.

33. The method of claim 32 wherein the elastase is human neutrophil elastase.

34. A composition comprising one or more compounds of claim 12 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12354

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 38/05, 38/06; C07K 5/062, 5/065, 5/078, 5/097
US CL :514/18, 19; 530/331; 544/30
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/18, 19; 530/331; 544/300

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, CHEMICAL ABSTRACTS
search terms: serine protease, elastase, inhibit, oxadiazole, thiadiazole, triazole, structures of claims 1 and 12

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,618,792 A (GYORKOS ET AL) 08 April 1997 (08/04/97), see columns 39-40, claims 1-7 and 9-12.	1-34
A	US 5,807,829 A (GYORKOS ET AL) 15 September 1998 (15/09/98), see claims 1-17.	1-11
A	US 5,861,380 A (GYORKOS ET AL) 19 January 1999 (19/01/99), see claims 13, 14, 43-68.	12-34

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
17 AUGUST 1999

Date of mailing of the international search report
09 SEP 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks

Authorized officer
L. Lawrence Tarazano